THE ORAL ADMINISTRATION OF ANTITOXINS.*

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THIS paper is a report of the later results of a series of investigations which were published in this *Journal*[1] in 1906. At that time our results warranted us in concluding that diphtheria and tetanus antitoxins, when given per mouth to experimental animals, were absorbed in sufficient quantities to protect those animals against several fatal doses of diphtheria and tetanus toxins. We were also able to show that the oral administration of antidiphtheric and antitetanic serums to children was followed by an absorption of the antitoxins, particularly that of diphtheria, in sufficient quantities to show markedly antitoxic properties in the blood of the treated individuals.

These results were obtained by the use of certain drugs which apparently inhibited digestion and promoted absorption. There was also reported some preliminary work showing that the toxins of diphtheria and tetanus were absorbed from the alimentary canal of guinea-pigs, provided that digestion was inhibited.

A series of five children were injected subcutaneously with from 320 to 1,040 units of diphtheria antitoxin, and careful tests showed that only a part of this could be detected in the blood of the treated individuals. A more direct comparison between the oral administration and the hypodermic injection could not be drawn. However, assuming that the antitoxin should be given to children as a prophylactic, we believed that the results obtained from the administration per mouth compared very favorably with those from subcutaneous injection.

After having carried on the work far enough to show that toxins and antitoxins, under certain conditions, are absorbed with a reasonable degree of uniformity when administered per mouth, we attempted to demonstrate more precisely the conditions necessary for such absorption. In our previous work it was found that the most uniform results were obtained when trikresol, salol, chloroform, and opium were

* Received for publication November 20, 1908.

[1] *Jour. Infect. Dis.*, 1906, 3, p. 701.

added to the antitoxins before administration per stomach. The question remained whether these were the best drugs to use and in what quantities they should be given. It also appeared to us that the absorption of diphtheria toxin, when administered per mouth, should be determined for the horse, to confirm and strengthen previous results and also to suggest a possible practical application of the oral method for immunization.

In our former report no definite conclusion could be drawn in regard to the rate of absorption of the antitoxins and toxins from the alimentary canal. This phase of the problem seems to us to be of considerable clinical importance.

It was also necessary to know from actual experiment whether dry serum could be given orally and absorbed with the same degree of uniformity as the liquid antitoxin. This we believe to be of practical consequence, if the oral method should ever be used as a prophylatic in children.

Finally we decided to conduct a series of experiments on children, treating some by hypodermic injection and others by oral administration of antitoxin and, by testing the blood of the children so treated for its antitoxic content, to be able to make a direct comparison between the two methods of treatment.

EXPERIMENTS RELATIVE TO THE NATURE AND QUANTITY OF DRUGS BEST ADAPTED TO THE PROMOTION OF ABSORPTION AND INHIBITION OF DIGESTION WHEN GIVEN ORALLY WITH ANTITOXIN OR TOXIN.

A series of 64 guinea-pigs were treated with tetanus toxin per stomach, and on this series various drugs in different combinations were tried. Likewise, a series of 12 guinea-pigs and seven rabbits, used for the same purpose, were treated per mouth with antitoxin. Some of the drugs which were tested on the above animals were atropine, codeine, hyoscyanine, morphine, cocaine, and sodium bicarbonate. These were tried to find out whether any one or several in combination would give better results than the opium, salol, and chloroform. Experiments were also conducted to ascertain whether opium, salol, or chloroform could be omitted.

The following series of 29 guinea-pigs were treated with dry

antitoxic serum, to which were added only opium and salol, the chloroform being eliminated. Twenty-seven of these animals were treated per mouth, each with 1 grm. of dry diphtheria antitoxin, to which was added 0.05 grm. of opium and 0.1 grm. of salol. Before treatment they received 5 c.c. of a 1 per cent solution of sodium bicarbonate. The series of pigs were then injected subcutaneously with 3.5 fatal doses of diphtheria toxin. The two control and four of the treated pigs died in two days. At the end of four days 17 of the treated pigs had died, and the remaining 10 out of 27 remained well. In the above experiment the series of pigs received a rather heavy dose of toxin, and the fact that 10 of the pigs withstood $3\frac{1}{2}$ fatal doses, shows considerable absorption of the antitoxin without the use of the chloroform.

In the next experiment sodium bicarbonate was given about one-half hour before the administration of the antitoxin, and much better results were obtained.

Table 1 gives the details of this series of experiments. A study of the table will show clearly that the administration of a sodium bicarbonate solution one-half hour before the toxin promotes absorp-

TABLE 1.

SODIUM BICARBONATE AS AN AID IN PROMOTING ABSORPTION OF ANTITOXIN.

One per cent sodium bicarbonate given one-half hour before animals were treated per stomach with toxins. Control animals treated with the same amount of toxin, prepared with the same amount of drugs, but sodium bicarbonate not given before treatment.

Animal Used	Material Used in Treating Animals	No. Control Animals. Not Treated with Sodium Bicarb. Before—All Lived	No. Animals Treated with Sodium Bicarb. ½ Hour Before Administration	No. Animals Treated with Sodium Bicarb. Which Died	No. Animals Treated with Sodium Bicarb. Which Lived
Guinea-pigs	Tetanus toxin 100×f. d.	1	3	1	2*
Guinea-pigs	Tetanus toxin 100×f. d.	4	2	1	1*
Rabbits	Diph. toxin 250×f. d.	3	1	1	0
Rabbits	Diph. toxin 250×f. d.	2†	1	1	0
Rabbits	Diph. toxin 500×f. d.	2§	1	1	0
Rabbits	Diph. toxin 500×f. d.	1	1	1	0

* Had marked symptoms and recovered. None of the pigs which did not receive the sodium bicarbonate showed symptoms.

† One of these rabbits died seven days after receiving the toxin. The rabbits treated with sodium bicarbonate, before administration of toxin, died two days after receiving the toxin.

§ Both of these died seven and eight days after receiving toxin. The rabbit treated with sodium bicarbonate died in two days.

tion probably by neutralizing the hydrochloric acid in the stomach and thus inhibiting digestion.

THE ABSORPTION OF TOXINS.

A series of 29 rabbits and 16 guinea-pigs were used in verifying former results and studying the absorption of diphtheria and tetanus toxins. The administration of snake venoms per mouth, with and without drugs, was tried on a series of 17 guinea-pigs. Three horses were treated with diphtheria toxin per stomach. The results of the work on the series of the 29 rabbits are given in Table 2. A study of the table will show that the results are, on the whole, fairly uniform and they confirm our previous observations that diphtheria toxin, under certain conditions, is absorbed from the alimentary canal. Some of the rabbits, given in Table 2, were used in testing different drugs and others in studying the rate of absorption.

TABLE 2.

DIPHTHERIA TOXIN, PER STOMACH, RABBITS.

Rabbit No.	No. Fatal Doses of Diphtheria Toxin	Drugs Added to Toxin	Result
Control 1	300	No drugs	Lived
" 2	500	" "	Dead 14 days
" 3	250	" "	Lived
" 4	None	Broth and drugs, same proportion as treated animals	"
" 5	"	Broth and drugs, same proportion as treated animals	"
6	300	Usual drugs	Dead 3 days
7	300	" " and atropine	" 2 "
8	500	" " without opium	" 10 "
9	500	" " with "	" 4 "
10	500	" " flushed out after 2 hrs.	" 1 "
11	500	" " not flushed out	" 1 "
12	250	" " Na_2Co_3 before	" 2 "
13	250	" "	" 7 "
14	250	" " Na_2Co_3 before	" 2 "
15	500	" " flushed out after 1 hr.	" 3 "
16	500	" " Na_2Co_3 before	" 3 "
17	500	" "	Lived, sick 3 days
18	500	" "	Lived
19	500	" " flushed out after 1 hr.	"
20	250	" " with sod. bicarb.	"
21	250	" " " " "	"
22	250	" "	"
23	500	" " flushed out after 1 hr.	"
24	400	" "	"
25	400	" "	"
26	200	" "	"
27	200	" " with codeine	"
28	200	" " " atropine	"
29	200	" " " hyoscyanine	"

In the same way 38 guinea-pigs were treated with tetanus toxin and the results were fairly consistent with those already obtained.

A series of guinea-pigs were treated per stomach with rattlesnake and cobra venoms. The results were positive. A few guinea-pig injections, subcutaneous, showed that 0.015 grm. of each venom would kill a 300 grm. pig in one hour. The results of the oral administration are given in Table 3.

TABLE 3.

No. of Pig	Snake Venoms		Per Stomach, Guinea-Pigs	
	Species of Venom	No. Grams of Venom Given	With or Without Usual Drugs	Results
1	Rattlesnake	0.1	Without	No symptoms
2	Cobra	0.1	"	"
3	Rattlesnake	0.1	With	Dead 30 hours
4	Cobra	0.1	"	" 4 "
5	Rattlesnake	0.05	"	" 24 "
6	Cobra	0.05	"	" 24 "
7	Rattlesnake	0.01	"	Symptoms 24 hrs. Recovery
8	"	0.01	Without	No symptoms
9	Cobra	0.01	With	" "
10	"	0.01	Without	" "
11	No venom, drugs alone			" "
12	" " " "			" "
13	Control not treated			Healthy

It will be seen, by reference to Table 3, that 0.1 grm. of either the rattlesnake or cobra venom, when given without drugs, produced no symptoms, while the same amount given with opium, salol, and chloroform killed in from four to 30 hours; 0.05 grm., given with drugs, killed in 24 hours; 0.01 grm., with or without drugs, failed to kill, although symptoms were produced in one pig 24 hours after receiving orally 0.01 grm. with drugs.

A series of experiments with the two vegetable poisons, abrin and ricin, with an extract of the poisonous mushroom, *Amanita phalloides*, and with the ptomaines from decayed beef, salmon, fish, and cheese gave negative results. All of these substances appeared to be absorbed, when given, either with or without drugs, to guinea-pigs per stomach, but absorption took place with no degree of uniformity.

The remainder of our work, relative to the absorption of toxins, has to do with the administration of diphtheria toxin to horses. In

all, three horses were treated per mouth with the toxin. The notes on these three cases are as follows:

Horse 1.—Brown gelding five years of age, thoroughbred running stock, appetite good, horse normal, except lameness of forelegs. Administered toxin each morning, dose of toxin for each administration being prepared by adding to it 5 c.c. of a saturated solution of salol in chloroform and eight minims of fluid opium. One-quarter grain of atropine sulphate was added and then omitted at times, and we concluded that it was of no apparent benefit. The treatment was given on an empty stomach, water given immediately after treatment, and no food for two or three hours. The toxin used had a strength of 0.5 per L+ dose. The following administrations were made:

August	29, 1906	10 c.c. toxin with drugs
"	30, 1906	25 " " "
"	31, 1906	50 " " "
September	1, 1906	75 " " "
"	2, 1906	100 " " "
"	3, 1906	150 " " "
"	8, 1906	20 " " "

On September 4, 50 c.c. of blood was taken from the animal. A test showed that it contained no antitoxin. On September 14, 17 days after beginning treatment, a sample of blood was drawn from the horse, and on being tested, showed a potency of less than 10 and more than five units per c.c. On September 3 the animal's temperature rose to 105°.6 F. and he was listless, ate but little, throat became sore. The temperature remained between 102° and 104° until September 9 when it fell to 100°, rising again on September 11 to 102°. On September 15 the horse died of general paralysis, believed to be due to the diphtheria toxin.

Horse 2.—Black gelding, 10 years old, strong, healthy, good appetite; treated with diphtheria toxin No. 08648, prepared as for horse 1; toxin given by special bottle and by stomach tube. Treatment begun on October 1. First dose 4 c.c., increased the dose to 100 c.c. on October 10, and to 225 c.c. on October 19. The animal was bled for sample on October 19 and tests showed that his serum contained nearly 25 units antitoxin per c.c. The animal was not taken off treatment before bleeding for test. On October 29 we began to give the animal a 10 per cent solution of sodium bicarbonate one-half hour before treatment with the toxin. The treatment was continued until November 10, when he received 1,000 c.c. of toxin. The treatment was then discontinued until November 20, when he was bled for test and then received 600 c.c. of toxin.

The test of the serum taken from the horse on November 20 gave a potency of between 50 and 100 units. The amount of toxin administered was increased from 600 c.c. on November 20 until, on Nov. 30, the animal received 1,300 c.c. During the night of November 30 the horse died. Careful post-mortem was made. The liver was very soft, and general pathological conditions, typical of those of horses treated with diphtheria toxins, were found. The temperature curves showed a regularity of response to increased dosage of the toxin as indicated by the temperature.

Horse 3.—Brown gelding, seven years old, in good, healthy condition. Began treatment December 12, 1906, with toxin-antitoxin mixture, L+ dose of toxin 0.5 c.c., antitoxin of 300-unit potency; gave drugs in same proportion as in two previous experiments; used fresh serum without preservative; no preservative in toxin.

On December 29, 18 days after beginning treatment, the horse suddenly died from asphyxia. Again we believed that death was produced from diphtheric paralysis. Some blood was collected from the jugular vein of the animal and, on being tested, showed a potency of between 300 and 350 units per c.c. It must be taken into consideration that the blood was taken from this horse and tested while he was receiving daily administrations of toxin, so that some toxin might have been present in the blood.

The above experiments show conclusively that diphtheria toxin, when given orally with drugs, is absorbed in sufficient quantities to produce in the blood of the horse a greater or less amount of antitoxin. The fact that horse 3, which died on the 18th day after treatment was begun, showed a potency of 300 units antitoxin per c.c. in his blood, might possibly indicate that had be been treated more slowly and lived, a high degree of potency would have appeared in his blood.

RATE OF ABSORPTION OF TOXIN AND ANTITOXIN FROM THE ALIMENTARY CANAL.

The rate of absorption was studied by the following methods:

1. By flushing out the alimentary canal with a comparatively large dose of sodium sulphate at varying periods of time after administration, per stomach, of diphtheria and tetanus antitoxins to guinea-pigs and diphtheria toxin to rabbits.

2. By the injection of toxin at varying periods of time after the oral administration of the specific antitoxin.

3. By the computation of the amount of unabsorbed antitoxin in the stomach of guinea-pigs at varying periods of time after the antitoxin was placed in the stomach.

4. By the oral administration of antitoxins to children and determination of the antitoxic content of the blood at varying periods of time after treatment.

Tables 4, 5, and 6 give the results of the experiments according to methods 1 and 2, enumerated above.

Eleven guinea-pigs were treated per mouth with 1 grm. dry diphtheria antitoxin, then the alimentary canal was flushed out with sodium sulphate at intervals of time, varying from one to six hours, after the administration. The purpose of this was to remove the unabsorbed antitoxin from the alimentary canal. The pigs were then injected with three fatal doses of toxin. Only two of these pigs died from the toxin, both having been treated with the purgative one hour after

TABLE 4.

RATE OF ABSORPTION.

Guinea-pigs, alimentary canal flushed out with sodium sulphate at varying periods of time after administration of antitoxins.

Group	Antitoxin Used Administration per Stomach	No. Fatal Doses of Toxin Injected	No. of Treated Pigs	No. of Control Pigs, All Dead	Periods of Time After Treatment Pigs Were Flushed with Sodium Sulphate	No. of Pigs Saved	Those Pigs Died Which Were Flushed After the Following Periods of Time
1	1 grm. dry diph. antitoxin	3	4	1	1, 3, 4, and 6 hours	3	1 hour
2	1 grm. dry diph. antitoxin	3	3	1	1½, 2½, and 4 hours	3	0
3	1 grm. dry diph. antitoxin	3	2	1	1 and 4½ hours	1	1 hour
4	1 grm. dry diph. antitoxin	2	2	1	2 and 3 hours	2	0

receiving the antitoxin. This experiment would indicate that within a little more than one hour a guinea-pig will absorb enough antitoxin from the stomach to protect it against three fatal doses of diphtheria antitoxin.

A glance at Table 5 will show that the same conditions hold true when rabbits are treated per mouth with diphtheria toxin and then flushed out with sodium sulphate one and two hours after the oral treatment.

TABLE 5.

RATE OF ABSORPTION (*continued*).

Rabbits flushed out with sodium sulphate, per stomach, at varying periods of time after treatment per stomach with large doses of toxin.

No. of Rabbits Treated	No. of Rabbits Flushed Out	Material Used	Periods of Time After Treatment Rabbits Were Flushed Out	Those Rabbits Lived Which Were Flushed After the Following Periods of Time	No. of Rabbits Not Flushed Out All Died
3	2	500 f.d. diph. toxin	1 and 2 hrs.	1 hour	1
3	2	500 " " "	1 and 2 hrs.	1 hour	1*

* Symptoms two days and recovered, a large, rather old animal.

Eleven pigs, Table 6, received, orally, diphtheria antitoxin and were injected with three fatal doses of the toxin as follows:

One hour before, at the same time, 1, 2, 3, and 24 hours after receiving the antitoxin. Eight of these pigs lived, and three which received the toxin subcutaneously at the same time as the antitoxin orally died from the injection of toxin. This result certainly tends to show that only a short time is necessary for sufficient absorption of antitoxin to take place to protect a guinea-pig against three fatal doses of toxin.

Another series of 11 pigs were treated per stomach with diphtheria antitoxin, then, after periods of time, varying from one to 25 hours, the pigs were killed, stomachs removed, and amount of albumens present determined. One grm. of the serum was given each pig. The amount of albumens present was obtained by precipitation with strong alcohol, filtering, drying the precipitate, and weighing. The weight of the albumens in 1 grm. of the dry serum, prepared as that given to the pigs, was 0.74 grm. We, therefore, used 0.74 grm. albumens as the amount each pig received when computing the results. One of the pigs of this series, No. 4 (110), was killed and stomach contents

TABLE 6.

RATE OF ABSORPTION.

Guinea-pigs, injected with toxin at varying periods of time during and after administration of antitoxin.

Group	Antitoxin Administered per Stomach	No. of Fatal Doses of Toxin Injected	No. of Treated Pigs	No. of Control Pigs. All Died	Periods of Time During and After Treatment per Stomach Pigs Were Injected with Toxin	Those Pigs Died Which Were Injected at the Following Times	No. of Pigs Saved
1	1 grm. dry diph. serum	3	6	1	1 hour before At same time 1, 2, 3, and 24 hours after	At same time	5
2	0 3 grm. dry tetanus antitoxin	2	1	1	3 hours after	0	1
3	tetanus antitoxin 40 units	2	4	2	At same time	2	2

washed out as was done in the case of each one of the treated pigs. The albumens from the stomach of this normal pig weighed 0.21 grm. Therefore, assuming that 0.21 grm. was the weight of the albumens from the mucus in the stomach of the treated pigs, we deducted that amount from the total weight of albumens in the computation of the amount of unabsorbed albumens in the stomach of the treated pigs.

These pigs, where not indicated otherwise on the table, were kept without food for 24 hours before treatment and were flushed out with sodium sulphate a few hours before treatment. Each pig, after being anesthetized, was opened through the abdominal wall, the stomach tied off at the pyloric and cardiac ends, and the antitoxin injected into the stomach through a very fine needle. At the time each pig was killed and stomach removed, a few c.c. of blood was collected and tested as to its antitoxic content. In every case the blood serum of these pigs contained some antitoxin and our results obtained by drying and weighing the albumens were confirmed.

Table 7 gives this experiment in detail. From 7.2 to 100 per cent of the antitoxic serum placed in the stomach was absorbed. These results substantiate those obtained by the two former methods. From the stomachs of two pigs there was absorbed, in a period of one hour, in one case 22.9 per cent and in the other 28.3 per cent of the total amount of albumens.

Table 8 gives the antitoxic content of the blood of all the people we have treated with antitoxin per mouth. This, with the period of time after treatment that the blood was collected from the individual, gives a basis for drawing conclusions as to the rate of absorption.

The blood for tests was drawn from these individuals in from 6½ hours to nine days after the oral administration of the antitoxin. A direct comparison cannot be made between results following shorter and longer periods of time for absorption.

Case 17, E. H., 16 years old, absorbed in 6½ hours 0.0269 per cent of the diphtheria antitoxin placed in his stomach, while Case 16, W. K., 16 years old, absorbed in 20 hours only 0.0077 per cent, and Case 11, 15 years old, absorbed 0.025 per cent.

The results point to the conclusion that antitoxin is absorbed in a relatively short time.

TABLE 7.

RESULTS TABULATED OF PRECIPITATION TESTS, FROM CONTENTS OF STOMACHS OF PIGS TREATED WITH 1 GRM. DRY DIPHTHERIA ANTITOXIN.

No. of Filter	Weight of Filter. Grms.	No. of Guinea-Pigs	Period of Time Prepared Serum Remained in Stomach	Weight of Dried Precipitate and Filter, Grms.	Weight of Dried Precipitate, 0.21 Grm. Deducted	Percentage of Albumens Absorbed	No. of Antitoxic Units Administered	No. of Antitoxic Units Absorbed	Results, Confirmed by Tests of Blood of Animal by Making Guinea-Pig Injections
2.....	3.11	1 (110)	1 hour	3.79	0.57	22.9 per cent	3,000	687	+
3.....	2.75	2 (110)	2 "	3.4	0.39	52.7 "	3,000	1,581	+
4.....	3.07	3 (110)	3 "	3.84	0.56	24.3 "	3,000	729	+
5.....	3.314	5 (110)	20 "	3.52	0	All	3,000	3,000	+
6.....	3.05	6 (110)	25 "	3.21	0	All	3,000	3,000	+
8*.....	2.82	1 (17)	1 "	3.76	0.53	28.3 per cent	3,000	849	+
9*.....	2.83	2 (17)	2 "	3.52	0.68	8.1 "	3,000	243	+
10*.....	3.00	3 (17)	3 "	3.85	0.64	13.5 "	3,000	305	+
11.....	3.22	2 (18)	2 "	4.117	0.687	7.2 "	3,000	216	+

* Pigs 8, 9, and 10 were not flushed out with sodium sulphate previous to experiment. All others were flushed out before experiment.

TABLE 8.

DIPHTHERIA AND TETANUS ANTITOXINS GIVEN PER MOUTH TO MAN.

Case	Age Years	Kind of Antitoxin	No. of Units Antitoxin Administered	No. of Units Absorbed and Contained in Total Quantity of Blood of Individual	Time After Administration Blood Was Drawn and Tested	Per cent of Antitoxin Absorbed, as Shown by Antitoxic Content of Blood
W. P. 1....	7	Diphtheria	6,000	245.0	9 days	0.0408
L. T. C. 2..	24	"	13,800	140.0	6 "	0.0101
E. H. 3.....	16	"	6,000	189.0	5 "	0.0315
E. S. 4.....	7	"	6,000	181.5	82 hours	0.0205
W. E. K. 5.	29	"	13,800	283.7	72 "	0.0092
W. K. 6....	15	"	13,800	128.3	72 "	0.0093
H. K. 7....	19	"	4,500	300.0	72 "	0.066
R. S. 8.....	7	"	3,000	421.0	24 "	0.14
E. H H. 9.	20	"	3,000	84.0	24 "	0.028
C. V. 10....	17	"	12,000	43.5	22 "	0.0036
E. P. 11....	15	"	3,000	75.2	22 "	0.025
G. L. 12 ...	15	"	3,000	261.5	22 "	0.087
B. S. 13 ...	7	"	3,000	562.5	20 "	0.187
A. M. 14...	17	"	3,000	151.5	20 "	0.0505
G. P. 15 ...	8	"	6,000	750.0	20 "	0.125
W. K. 16 ..	16	"	12,000	93.2	20 "	0.0077
E. H. 17 ...	16	"	3,000	80.8	6½ "	0.0269
E. A. 18 ...	16	Tetanus	1,500	0.0000045	9 days	0.0000003
W. K. 19...	16	"	600	0.000003	72 hours	0.000000005
W. E. K. 20	29	"	1,500	0.0000015	72 "	0.00000001
L. T. C. 21	24	"	900	0.000001	60 "	0.00000001
B. P. 22 ...	5	"	600	0.000002	48 "	0.000000003
F. G. 23. ..	7	"	400	0.003418	20 "	0.00000852

THE ABSORPTIONS OF DRY ANTITOXINS.

We thought it desirable to see if the antitoxins of diphtheria and tetanus would be absorbed from the stomach equally as well when dry as when liquid. This is of practical importance, should antitoxin ever be administered per mouth because:

1. The dry antitoxin will remain permanent indefinitely.

2. It is very much less expensive to manufacture.

3. It could be kept in stock and in the medicine case and conveniently administered by the physician.

4. The dry antitoxin could be taken with no difficulty or unpleasantness by the patient.

Much of the work in the experiments already described has been done with the dried serums. Table 9 gives the results of the administration of dry antitoxin to guinea-pigs, per mouth. In Table 9 it is shown that 46 out of 53 pigs, treated with dry diphtheria antitoxin, were saved from death after the injection of three fatal doses of toxin. Thirteen control pigs all died in less than four days. Likewise, out of 18 pigs treated per mouth with tetanus antitoxin, only one was lost after the series were injected with 2 and 2.5 fatal doses of tetanus

toxin. We can safely state that the dry antitoxin is absorbed equally as well as the liquid serum.

TABLE 9.

DRY DIPHTHERIA ANTITOXIN, PER STOMACH, GUINEA-PIGS.

Group	Amount in Grms. Dry Serum Given	No. of Fatal Doses of Toxin Injected	No. of Pigs in Group	No. of Control Pigs in Group All Died	No. of Treated Pigs in Group	No. Treated Pigs Saved	No. Treated Pigs Lost
3.....	0.5	3	7	2	5	5	0
4.....	1	3	3	1	2	2	0
6.....	1	3	6	1	5	4	1*
7.....	1	3	4	1	3	3	0
9.....	1	3	9	1	8	7	1*
10.....	1	3	8	1	7	6	1*
11.....	0.1 and 0.3	3	3	1	2	2	0
12.....	0.05 to 0.2	3	6	1	5	4	1
13.....	0.01 to 0.05	3	6	1	5	4	1
14.....	0.03 to 0.05	3	4	1	3	2	1
15.....	0.03 to 0.5	3	10	2	8	7	1
						46	7
DRY ANTITETANIC SERUM, PER STOMACH, GUINEA PIGS.							
2.....	1	2	4	1	3	3	0
3.....	0.2 to 0.3	2	4	1	3	3	0
4.....	1	2	5	1	4	4	0
7.....	0.1 to 0.3	2.5	4	1	3	2	1
8.....	0.1 to 0.5	2.5	6	1	5	5	0
			23	5	18	17	1

* These pigs were used in testing rate absorption and were flushed out one hour after giving the antitoxin per stomach.

ORAL ADMINISTRATION OF ANTITOXINS IN MAN.

Since the publication of our last report experiments have been continued with diphtheria and tetanus antitoxins, relative to their administration per mouth and absorption in children. In that paper we reported the results of the oral administration of the antitoxin to a series of 14 persons, whose ages were from five years to 29 years. From 3,000 to 13,800 units of diphtheria and 600 to 1,500 units of tetanus antitoxins were given to these individuals per mouth. Nine of these 14 persons received, orally, the diphtheria antitoxin, and guinea-pig tests demonstrated the presence of antitoxin in the blood in amounts which averaged 0.05 unit antitoxin per c.c. of the total blood in the body, while the five who were given the tetanus antitoxin averaged 0.0000024 unit per c.c. of total blood. Owing to the insufficient quantities of blood to carry on complete tests, the maximum amount of antitoxin was not demonstrated except in three of the cases. Therefore the above averages do not represent the maxi-

mum amount of antitoxin that was absorbed after the oral administrations.

Five individuals, who received subcutaneous injections of diphtheria antitoxin in quantities of from 320 to 1,040 units, showed, by guinea-pig tests, an average of 0.19 unit per c.c. of body blood. It was impossible, however, to make a direct comparison of the two methods because the maximum amount of antitoxin absorbed after the oral administration was not determined.

In the present work we have endeavored to reach definite conclusions, by making a direct comparison of the two methods. The following series of experiments were conducted in the same manner as described in our former report:

> The individual under treatment was bled from the median cephalic vein before treatment with the antitoxin. The serum was collected from this blood and, together with a given number of fatal doses of toxin, was injected subcutaneously into guinea-pigs. Each individual under treatment then was either treated per mouth or was injected subcutaneously with a given amount of antitoxin and, after a few hours, the blood was again collected as before and tested as to its protective influence against the toxin in question, by injecting guinea pigs with the blood serum and toxin. A comparison of these results with those from injections of the human blood serum, before the individual was treated per mouth or subcutaneously, indicated whether the antitoxin which had been administered to the individual had resisted digestion and had been absorbed in sufficient quantities to cause the protective antitoxin to be present in the blood of the individual. The maximum amount of absorbed antitoxin, as indicated by the antitoxic content of the blood, was determined in each case. Tables 10 and 11 give in detail the results of these experiments.

In Tables 10 and 11, in the second column, under "guinea-pig injections" etc., the + and − signs indicate the range within which the toxic dose for a 250 grm. pig was determined. As, for example, Case 1 (E. H.), Table 10, the amount of diphtheria toxin necessary to kill a 250 grm. pig which was injected with 0.2 c.c. of the blood serum from E. H. after treatment with antitoxin per mouth lies between 12 and 15 fatal doses. In determining the amount of antitoxin absorbed, however, the number of fatal doses which was known to be neutralized by the given amount of human blood serum was used as a basis of computation in finding the number of units of antitoxin per c.c. in the blood of the individual. Thus, in the above illustration, Case 1 (E. H.), 12 times the fatal dose of toxin was taken as the maximum amount of toxin a 250 grm. pig would withstand when protected by 0.2 c.c. of the serum of E. H.

In Table 11 the average absorption per c.c. of body blood should be taken from Cases 1 to 8 in order to make a direct comparison with the average absorption of the eight cases, treated orally, given in Table 10. The reason for this is that no check tests were made for the antitoxic content of the serum of Cases 9 to 13 (Table 11) before injection with the antitoxin. Therefore, the antitoxic content of the blood of Cases 9 to 13, as indicated on the table, are probably, in reality, considerably less. A glance at Cases 1 to 8, in both Tables 10 and 11, will show that normal human serum, before the administration of diphtheria antitoxin, gives some protection against the toxin. The degree of this protection varies within comparatively wide limits.

The eight individuals who received the serum per mouth (Table 10) were treated as follows:

One-half hour before taking the serum, the individual drank a half-glass full of a 1 per cent solution of sodium bicarbonate. The dry antitoxin was dissolved in a sufficient amount of water and to it was added one minim of fluid opium (containing 22 grains crystallized morphine in each fluid ounce, and four times stronger than Tincture opium U. S. P.), and 4 to 10 minims of a saturated solution of salol in chloroform.

Assuming that the oral method of administration is of advantage as a prophylactic in children, we are confronted with the question, What is the most convenient and practical form in which to administer the serum and drugs? We are convinced that antitoxin may be used in the dry form. How the necessary drugs should be combined with the serum and whether the preparation should be given to the patient in the dry form inclosed in a capsule or made into a tablet, or whether it should be dissolved in water, are questions for the clinician.

A careful comparison of the two methods of administration and results of the actual trial, as shown in Tables 10 and 11, demonstrates that the oral treatment with antitoxin is effective. Our experiments warrant us in concluding that, in the case of children, the oral administration is followed by rapid absorption, almost as complete absorption as that following the hypodermic injection. Moreover, we do not hesitate in stating that the oral method is safer than the hypodermic method of administration. We have not observed any untoward effects in a single one of the 24 cases that we have treated orally.

A study of Table 12 shows the number of antitoxic units that should theoretically have appeared in the blood and the number of

TABLE 10.

DIPHTHERIA ANTITOXINS, PER MOUTH, MAN.

CASE	SEX	AGE	ANTITOXIN	NO. UNITS ANTITOXIN ADMINISTERED	GUINEA-PIG INJECTIONS BEFORE ADMINISTRATION OF ANTITOXIN TO FIND HOW MUCH PROTECTION, IF ANY, EXISTED IN THE HUMAN SERUM. ALL PIGS DIED		GUINEA-PIG INJECTIONS AFTER ADMINISTRATION OF ANTITOXIN SHOWING MAXIMUM PROTECTION IN BLOOD OF INDIVIDUAL. ALL PIGS LIVED		RESULTS		
					No. c.c. of Human Serum	No. Fatal Doses Toxin	No. c.c. of Human Serum	No. Fatal Doses Toxin	Period of Time After Administration Test Was Made for Antitoxic Content of Blood	No. Units Antitoxin in 1 c.c. of Blood	No. Antitoxin Units Absorbed and Contained in Total Quantity of Blood
E. H. 1....	Male	16	1 grm. Diphtheria	3,000	0.5	10	0.5	−15 +12	6½ hours	0.04	74.6
G. T. 2....	"	15	"	3,000	0.5	18	0.5	−35 +30	22 "	0.24	261.5
E. P. 3....	"	15	"	3,000	0.5	3	0.5	−10 + 5	22 "	0.04	75.2
C. V. 4....	"	17	"	3,000	1	3	0.5	− 5 + 4	22 "	0.02	43.5
W. K. 5....	"	16	"	3,000	0.5	3	0.5	− 6 + 5	20 "	0.04	93.2
G. P. 6....	"	8	"	3,000	0.5	10	0.5	−35 +30	20 "	0.4	750
B. S. 7....	"	7	"	6,000	0.5	12	0.2	−25 +18	20 "	0.3	562.5
A. M. 8....	"	17	"	3,000	0.5	3	0.5	− 6 + 5	20 "	0.02	151.5
									Average	0.1375	251.5

TABLE 11.

DIPHTHERIA ANTITOXIN, SUBCUTANEOUS INJECTION, MAN.

CASE	SEX	AGE	WEIGHT GRMS.	ANTI-TOXIN	NO. UNITS ANTITOXIN INJECTED	GUINEA-PIG INJECTIONS BEFORE INJECTION OF ANTITOXIN TO FIND HOW MUCH PROTECTION, IF ANY, EXISTED IN THE HUMAN SERUM. ALL PIGS DIED		GUINEA-PIG INJECTIONS AFTER INJECTION OF ANTITOXIN SHOWING MAXIMUM PROTECTION IN BLOOD OF TREATED INDIVIDUALS. ALL PIGS LIVED		PERIOD OF TIME AFTER INJECTION TEST WAS MADE FOR ANTITOXIC CONTENT OF BLOOD	NO. OF ANTITOXIC UNITS IN 1 C. C. OF BLOOD	NO. OF ANTITOXIC UNITS ABSORBED AND CONTAINED IN TOTAL QUANTITY OF BLOOD
						No. c.c. Human Serum Injected	No. Fatal Doses of Toxin	No. c.c. of Human Serum	No. Fatal Doses of Toxin			
E. K. 1...	Male	7	20.515	1 gram	3,000	0.2	15	0.2	−35 +30	24 hours	0.75	1280.7
L. 2.....	"	6	14.547	1 "	3,000	0.2	20	0.2	−35 +30	24 "	0.5	606.1
E. 3.....	"	8	21.634	½ "	1,500	0.2	10	0.2	−18 +16	72 "	0.3	540.8
H. 4.....	"	8	16.039	½ "	1,500	0.2	6 −6 +5	0.2	− 7 + 6	6 "	0.05	66.7
N. 5.....	"	9	26.110	1 "	3,000	0.2	18	0.2	−25 +20	20 "	0.1	217.5
W. 6.....	"	7	17.904	1 "	3,000	0.2	7	0.2	−10 + 7	20 "	0.05	74.6
B. 7.....	"	8	20.515	1 "	3,000	0.2	7	0.2	−20 +15	20 "	0.4	683.8
H. A. 8...	"	10	22.500	2 "	6,000	0.2	8	0.2	−16 +14	20 "	0.3	562.5
Five cases, the antitoxic properties of blood before injection not determined										Average	0.306	
F. 9.....	Male	7	27.272	Liquid	1,040	Not determined		1	−20 +12	24 hours	−0.2	454.7
B. 10.....	"	7	24.500	"	1,040	"	"	1	−12 + 7	15 days	−0.12	244.9
H. 11.....	"	7½	27.000	"	480	"	"	1	−12 + 7	24 hours	−0.12	270
E. 12.....	"	7	23.181	"	320	"	"	1	−15 +14	24 "	−0.15	289.7
B. Y. 13...	"	7	23.591	"	1,040	"	"	1	−38 +30	24 "	−0.38	747.7
										Average	0.194	

units that actually was found in the case of those individuals who received subcutaneous injections of the antitoxin. The average number of units absorbed and present in the blood of the eight individuals treated per mouth (Table 10) was 0.1375 unit per c.c. The average number of units per c.c. of blood of those individuals who received the subcutaneous injection of the antitoxin was 0.306. The ages of those who received the oral administrations varied from seven to 17 years, there being only two cases who were under 15 years of age. On the other hand, those who received the hypodermic treatment were all under 10 years of age. If all of the eight cases treated per mouth had been children under 10 years of age, we would expect to find a larger average amount of antitoxin absorbed per c.c. of the body blood. This fact gives the advantage, in making this direct comparison, to the subcutaneous method. Unfortunately, at the time we made the test of the oral method, as indicated in Table 10, we were unable to secure many children under 10 years. As the results of this comparison stand, however, we feel sure that, under proper conditions, enough antitoxin is absorbed from the stomach of a child to protect the child against subsequent infection.

TABLE 12.

SUBCUTANEOUS INJECTION, DIPHTHERIA ANTITOXIN, MAN.

Relation of amounts actually absorbed, as shown by antitoxic content of the blood, to amounts which, theoretically, should have been absorbed.

Case	Weight Grms.	No. of Units Antitoxin Injected Subcutaneously	No. of Units That Should Theoretically Have Been Absorbed per c.c. in Body Blood	No. of Units per c.c. Actually Absorbed and Present in Body Blood	No. of Units per c.c. not Absorbed	Percent of Antitoxin Absorbed per c.c. Body Blood
E. K. 1	20.515	3,000	1.75	0.75	1	42
L. 2.....	14.547	3,000	2.47	0.5	1.97	20
E. 3.....	21.634	1,500	0.82	0.3	0.52	36
H. 4.....	16.089	1,500	1.12	0.05	1.07	4
N. 5.....	26.110	3,000	1.37	0.1	1.27	72
W. 6.....	17.904	3,000	2.01	0.05	1.96	2
B. 7.....	20.515	3,000	1.75	0.4	1.35	22
H. A. 8	22.500	6,000	3.17	0.3	2.87	9
F. 9	27.272	1,040	0.46	0.2	0.26	43
B. 10.....	24.500	1,040	0.50	0.12	0.38	24
H. 11	27.000	480	0.21	0.12	0.09	57
E. 12.....	23.181	320	0.16	0.15	0.015	90
B. Y. 13 ..	23.591	1,040	0.52	0.38	0.14	73
Average....	21.954	2,147	1.25	0.26	0.99	38

CONCLUSIONS.

1. Toxins and antitoxins when given by mouth are usually rendered inert by the digestive processes. Their therapeutic or immunizing value is uncertain and not to be relied upon.

2. If digestion is inhibited, which may be readily accomplished by the use of appropriate drugs, toxins and antitoxins are absorbed unchanged and apparently in sufficient quantity and with such uniformity as to warrant the use of this method for therapeutic and immunizing purposes.

3. In treating children with antitoxin per mouth, the following method has given uniform and satisfactory results. One-half hour before administering the serum the child is given one glass of 1 per cent sodium bicarbonate solution. When the antitoxin is given there is added to it one minim of Fl. Ext. Opii and from four to 10 minims of saturated solution of salol in chloroform. When possible no food should be given for at least four hours before administering the serum.

4. In the 19 children and the hundreds of animals used in these experiments, there was no evidence of any "serum sickness" or anaphylaxis.

5. In our opinion the oral method of administering antitoxins of tetanus and diphtheria is the preferable one for prophylaxis.

a. On account of the absence of danger and the ease of administration.

b. Because the cost may be very materially lessened.

6. The hypodermic method of administering sera for curative purposes is the only one to be recommended unless extensive clinical experience should show that the oral method is equally efficacious.

7. A relatively high degree of immunity may be produced in animals by the oral administration of toxins if the absorption of the same is promoted by such means as we have suggested.